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The Examiner rejected claims 30-35 for reasons of record set forth in Paper No. 16, pages 3-5. The Examiner stated that newly added claims are also rejected over '335 because '335 also teach an expression vector comprising DNA encoding CD4-IgG (col. 11, lines 16-30 and col. 12, line 49 to col. 13, line 10), a method of producing CD4-IgG (col. 14, lines 29-42), and a method of producing CD4-IgG in CHO cells (col. 12, lines 65-66). The Examiner therefore stated that it would have been obvious to one having ordinary skill in the art at the time the invention was made to follow the teachings and motivations of '335 to make any CD4-IgG homodimer, including the claimed CD4-IgG2 homodimer, using an expression vector comprising DNA encoding CD4-IgG2, and to use host cells comprising this expression vector to produce CD4-IgG2 in CHO cells, as suggested by '335.

The Examiner stated that applicants' arguments filed 19 May 1997 have been fully considered, but they are not persuasive.

The Examiner stated that applicants argue that there is no close structural similarity between the CD4-IgG1 exemplified by '335 and the CD4-IgG2 taught by applicants, nor that any of the molecules taught by Capon exhibits sufficient close structural similarity to that instantly claimed. The Examiner stated that applicants also assert that Capon does not teach or suggest applicants' polypeptide. However, the Examiner further stated that Capon specifically teaches a CD4-IgG2 fusion protein (col. 7, lines 47-49). Capon also exemplifies a CD4-IgG1 fusion protein which is structurally almost identical to CD4-IgG2. The Examiner stated that both the instantly claimed CD4-IgG2 and the CD4-IgG1 taught by Capon appear to have identical CD4 extracellular domains comprising the N-terminal domain of the homodimer, and differ only in that the C-terminal domain of the homodimer is IgG1, in the case of Capon, or

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IgG2, in the instant case. The Examiner stated that it was well-known in the art at the time the invention was made that the constant domains of IgG1 and IgG2 are both structurally and functionally related to one another, and have a sequence identity of about 95% (see 5,431,793, col. 7, lines 42-44).

The Examiner stated that applicants assert that the disclosure of Capon of a method for producing the CD4-IgG2 is not a proper basis for determining whether the claimed compound is obvious. The Examiner stated that this argument is unpersuasive because Capon's method was not the basis of obviousness. Instead, Capon's express teaching that suitable fusion proteins are obtained from IgG2 is the basis. The Examiner stated that this teaching was pointed to in the rejection of record, Pater No. 16, page 4, lines 3-5. The Examiner stated that it is the composition itself that is suggested by Capon. The Examiner stated that Capon disclosed a motivation for producing the claimed fusion protein (col. 1, lines 11-15 and col. 10, line 66 to col. 11, line 4; also see discussion in Paper no. 16, page 4) and also provides a method for producing the CD4-IgG2 DNA, vectors, host cells, method of producing the protein recombinantly and the protein itself. Thus, the Examiner stated that Capon provides not only a teaching for the composition CD4-IgG2, but also a method for producing the claimed compound and a reasonable expectation of success since Capon exemplifies CD4-IgG1, a highly structurally and functionally similar compound.

The Examiner stated that applicants urge that there is no reasonable expectation of success in obtaining a functional CD4-IgG2 because of the amino acid differences between CD4-IgG1 and CD4-IgG2. However, as discussed above, since IgG1 and IgG2 are virtually identical in their constant domains, the Examiner stated that one having ordinary skill in the art would have the reasonable

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expectation that one could substitute the constant domain of IgG2 for that of IgG1 in the molecule taught by Capon and retain the functional properties of the fusion protein, especially since Capon specifically teaches that the constant domain of any IgG isotype could be used. In addition, the Examiner stated that there is no requirement under 35 U.S.C. §103 that there be absolute predictability of success, but rather only a reasonable expectation of success in producing an obvious variant of a known compound.

The Examiner stated that applicants lastly argue that there is no motivation to make the specific amino acid alterations between CD4-IgG1 and CD4-IgG2. The Examiner stated that this argument is unpersuasive because the only differences in amino acid sequence between CD4-IgG1 and CD4-IgG2 are those amino acid residues which differ between the constant domains of IgG1 and that of IgG2. The Examiner stated that since Capon suggests a CD4-IgG2 fusion protein, those minor amino acid sequence differences between CD4-IgG1 and CD4-IgG2 were known by Capon or by any one having ordinary skill in the art. Thus, the Examiner stated that one having ordinary skill in the art following the teachings of Capon would have produced a CD4-IgG2 with the same specific amino acid alterations as that instantly claimed.

In response, applicants respectfully traverse the examiner's above rejection. Applicants respectfully maintain that their claimed invention is structurally distinct from Capon. In addition, applicants contend that one would not arrive at the claimed invention by following the teachings of Capon.

Applicants point out that the claimed invention uses gamma2 whereas the Capon group uses gamma1. Without conceding the correctness of the Examiner's position, applicants contend that even if one were

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to read Capon to say that it teaches the use of gamma2, the result would still be different from the claimed invention. Applicant points out that there are two components of the construct: (1) CD4 portion; and (2) Ig portion. The flexibility in creating the construct resides in where the joint between the two portions is made. Accordingly, one must examine the amino acid residues which reside at the C-terminus of CD4 and at the N-terminus of Ig. The claimed construct has a different C-terminus at the CD4 portion and a different N-terminus at the Ig portion.

The CD4 portion used by Capon is 180 amino acids in length with a C-terminus of glutamine at position 180. See Figure 1 of Byrn et al, "Biological properties of a CD4 Immunoaderhesin," Nature 344: 667 (1990) which was authored by the Capon group, a copy of which was presented as Exhibit 15 of the information disclosure statement. In contrast, the CD4 portion of the claimed invention is 179 amino acids in length with a C-terminus of phenylalanine at position 179.

With respect to the Ig portion, applicant's construct differs from Capon's. Capon deletes five amino acids from the hinge region. One of these residues is a Cysteine which could play a role in increased dimerization through disulfide bonding. Thus, one would read Capon as teaching the removal of the first five amino acids from the hinge. In contrast, applicants construct contains the entire hinge including this Cysteine residue. See page 10, lines 25-35 of the originally-filed specification.

Thus, Capon's construct is four amino acids shorter. Capon has an additional residue in the CD4 region but 5 fewer residues in the Ig hinge region. Thus, the constructs are structurally distinct.

The above might lead one skilled in the art to question how much

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variation could be introduced when making these constructs. However, there is no teaching in Capon as to how the constructs might be varied. Accordingly, by reading the references, would adopt a strict literal interpretation and follow the teachings exactly. Thus, one would not be led to use a shorter CD4 region nor a longer Ig region containing the entire hinge. As was used in applicants's construct. Since there is no such teaching or suggestion, then applicant's claimed invention was not obvious.

In addition, applicants point out that the only time that Capon does utilize gamma2 (instead of gamma1) he includes only the V1 region of CD4. In contrast, the claimed invention utilizes both V1 and V2. Capon does not suggest that there would be a problem with using only V1. Accordingly, it would not have been obvious to create the claimed construct consisting of both V1 and V2. Thus, this demonstrates a further difference between Capon's construct and the claimed invention.

Applicant's claimed invention is directed to specific CD4-IgG2 chimeric proteins. The cited references cannot render applicant's claimed invention obvious because they teach away from the claimed invention.

Capon named the chimeric CD4 immunoglobulin protein as Immuno adhesins "because they contain part of an adhesive molecule linked to the immunoglobulin Fc effector domain." see page 526, first column, lines 2-4. Applicant's claimed invention is to incorporate the Fc portion of IgG2 to minimize Fc-mediated functions.

In addition, applicants respectfully direct the Examiner's attention to Chamow et al (exhibit 16 of the information disclosure

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statement). This paper continued the teachings of Capon et al, and direct the art away from using the class of Ig which will minimize Fc-mediated functions. In fact, this group has provided other papers which teach the same doctrine. Applicants also direct the Examiner's attention to another paper by the same group entitled "Biological Properties of a CD4 Immunoaderisin" Nature vol. 344, 1990, pages 667-670 (Exhibit 15 of the Information Disclosure Statement). Applicants point out that only IgG1 was used to make the "Immunoaderisin."

Traunecker et al (Exhibit 25 of the Information Disclosure Statement) used mouse IgM and mouse gamma2A to make CD4 chimerics. Mouse immunoglobulin subclasses are different from human immunoglobulin subclasses. Both of the chimerics (CD4-mouse IgM and CD4-mouse IgG2) bind to Fc receptor. See Traunecker, page 96, first column, third paragraph, firstline, and Figure 3C. In addition, Traunecker teaches the use of mouse-IgM for the CD4 chimeras. It discourages ordinary skilled artisans to use any other Ig class. See abstract, lines 13-14 which recites "we find that the pentameric CD4-IgM chimera is at least 1000-fold more active than its dimeric CD4-IgG counterpart in synctium inhibition assays.."

Accordingly, an ordinary skilled artisan will use other Ig subclasses to solve the objective technical problem and will most likely focus on "Immunoaderisin" or the IgM subclass. Applicants note that Zettlmeissl (Exhibit 26 of the Information Disclosure statement), which cites both Capon et al and Traunecker et al, uses only IgG1 and IgM in its experiments. Accordingly, applicants maintain that the claimed invention is not obvious in light of the cited reference.

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Furthermore, applicant respectfully points the Examiner's attention to page 10, line 20 to page 11, line 10 of the specification which teaches that the CD4-gamma2 chimeric heavy chain homodimer provides advantages relative to the CD4-IgG1 heavy chain homodimers. These gamma2 homodimers are efficiently assembled intracellularly and efficiently secreted from mammalian cells as a homodimer, enabling high recovery and purification from the medium. This is in contrast to the Capon CD4-IgG1 construct which results in poor secretion and recovery from cell culture medium of the recombinant molecule. The entire hinge domain of gamma2 heavy chain was included to provide efficient dimerization since the cysteine residues in this domain form the disulphide links to the second chain of the homodimer, positioning the two chains in the correct spatial alignment and facilitating formation of the antigen combining site.

Applicant also points out that their claimed invention provides unexpected results as follows:

1. Pharmacokinetics of CD4-IgG2 vs CD4-gamma1 in humans:

See Exhibit 1 In each case, the protein was administered by intravenous injection to HIV-positive adults. Serum samples were obtained at the indicated time points and analyzed by ELISA for CD4-IgG2 or CD4-gamma1 concentration. Equivalent or lower doses of CD4-IgG2 yielded higher serum concentrations at all time points examined. This clearly shows that compared with the CD4-gamma-1 construct, the claimed construct has improved pharmacokinetics, including higher peak serum concentrations and area under the serum concentration-time curve (AVC)

2. HIV-1 Neutralization Studies:

CD4-gamma2 was tested for its ability to neutralize HIV-1

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in vitro, using a laboratory-adapted strain and a primary isolate of HIV-1. 50 tissue culture infectious doses of the laboratory-adapted strain HIV-1<sub>LAI</sub> or the primary isolate HIV-1<sub>JR-CSF</sub> were incubated with either CD4-gamma2 or sCD4. The mixtures were then added to PHA-activated normal donor peripheral blood mononuclear cells. The cultures were initially washed and then later the cellular supernatants were assayed for p24 core antigen expression. Applicant attaches hereto as Exhibit 2 a chart which compares sCD4 with CD4-gamma2. These results demonstrate that CD4-gamma2 neutralizes the isolates more potently than does sCD4. Moreover, applicant attaches hereto as Exhibit 3 the reference by Gauduin et al entitled "Effective Ex Vivo Neutralization of Human Immunodeficiency Virus Type 1 in Plasma by Recombinant Immunoglobulin Molecules, Journal of Virology, vol. 70, no. 4 (1996) which shows that CD4-IgG2 was observed to be significantly more potent than sCD4 in neutralizing ex vivo the uncloned viral quasispecies present in HIV<sup>+</sup> patient plasma. Furthermore, applicant attaches hereto as Exhibit 4 the reference entitled "Designing CD4 Immuno adhesins for AIDS Therapy" by Capon et al, Nature 337: 525 (1989) which demonstrates on page 529, last paragraph that sCD4 and CD4-gamma1 have similar neutralizing activity. Since sCD4 and CD4-gamma1 have similar activity and since CD4-gamma2 is more potent than sCD4, then one would conclude that CD4-gamma2 is more potent than CD4-gamma1. Accordingly, this shows unexpected results for the claimed construct in comparison to that in the cited reference.

Applicant respectfully contends that this data shows that the homodimers and heterotetramers yield unexpected results. Accordingly, applicant contends that these remarks obviate the

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above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Accordingly, in view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Respectfully submitted,

Albert Wai-Kit Chan

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

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